PATENT COOPERATION TREATY

RECEIVED
COZEN IP DEPT.

JUL 28 2004

From the INTERNATIONAL SEARCHING AUTHORITY

N.B.

To:
COZEN O'CONNOR
1900 MARKET STREET
PHILADELPHIA, PA 19103

RECEIVED
AUG 2 2004

PCT

DUE DATE 9-23-04
MAX DATE
DOCKETED BY (m)

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Supp. IDS due 8-23-04 (m)

	Date of Mailing (*day/month/year*)
Applicant's or agent's file reference ISIS0048-500 136453	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US03/12544	International filing date (*day/month/year*) 21 April 2003 (21.04.2003)
Applicant ISIS PHARMACEUTICALS, INC.	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Dorothea Lawrence for Sean R McGarry Telephone No. 703 308-0196

Form PCT/ISA/220 (April 2002) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
COZEN O'CONNOR
1900 MARKET STREET
PHILADELPHIA, PA 19103

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

	Date of Mailing (*day/month/year*) 23 JUL 2004
Applicant's or agent's file reference ISIS0048-500	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US03/12544	International filing date (*day/month/year*) 21 April 2003 (21.04.2003)
Applicant ISIS PHARMACEUTICALS, INC.	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Sean R McGarry Telephone No. 703 308-0196

Form PCT/ISA/220 (April 2002) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ISIS0048-500	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/12544	International filing date *(day/month/year)* 21 April 2003 (21.04.2003)	(Earliest) Priority Date *(day/month/year)* 19 April 2002 (19.04.2002)
Applicant ISIS PHARMACEUTICALS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 14 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the Report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   ☒ contained in the international application in written form.
   ☒ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ **Certain claims were found unsearchable** (See Box I).
3. ☒ **Unity of invention is lacking** (See Box II).
4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ____
   ☐ as suggested by the applicant.
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.
   ☐ None of the figures

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/12544

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1, 2, 3 (limited to SEQ ID NO: 20), and 4-20

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/12544

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 21/04; A61K 48/00; C12N 15/00
US CL : 435/375; 536/24.5; 514/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/375; 536/24.5; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
West, MEDLINE, BIOTECHNO, CAPLUS, SCISEARCH, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	SOUNESS et al. 11-betea-Hydroxysteriod Dehydrogenase Antisense Affects Vascular Contractile Response and Glucocorticoid Metabolism. Steroids. March 2002, Vol. 67, pages 195-201, see entire document.	1, 2, 4, 5, 11, 12, 14, 15 --- 6-9, 13, 16-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
31 March 2004 (31.03.2004)

Date of mailing of the international search report
23 JUL 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Sean R McGarry

Telephone No. 703 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

This international searching authority has found 84 inventions claimed in the International Application covered by the claim(s) indicated below:

Claim 3 specifically claims 84 different antisense oligomers by SEQ ID NOS, which are targeted to and modulate the expression of hydroxysteriod 11-beta dehydrogenase 1.

This international searching authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2, and 13.3) for the reasons indicated below:

According to the guidelines in Section (f)(i)(a) of Annex B of the PCT Administrative Instructions, the special techincal feature as defined by PCT Rule 13.2 shall be considered to be met when all the alternatives of a Markush-group are of similar nature. For chemical alternatives, such as the claimed antisense sequences, the Markush group shall be regarded as being of similar nature when
(A) all alterntives have a common property or activity and
(B)(1) a common structure is present, i.e, a signficant structure is shared by all of the alterrnatives or
(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to an art recognized class of compounds in the art to whcih the invention pertains.

The instant antisense sequences are considered to be each separate inventions for the following reasons:

The sequences do not meet the criteria of (A), common property or activity or (B)(2), art recognized class of compounds. Although the sequence target and modulate expression of the same gene, each antisense sequence behaves in a different way in the context of the claimed invention. Each sequence targets a different and specific region of the targeted gene and each sequence modifies (either increases or decreases) the expression of the gene to varying degrees (per Applicants' Tables 1 and 2, for example). Each member of the class cannot be substituted, one for the other, with the expectation that the same intended result would be acheived.

Further, although the sequence target the same gene, the sequences do not meet the criteria of (B)(1), as they do not share, one with another, a common core structure. Accordingly, unity of invention between the antisense sequences is lacking and each antisense sequence claimed is considered to constitute a special technical feature.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

ELSEVIER

Steroids 67 (2002) 195–201

Steroids

11β-Hydroxysteroid dehydrogenase antisense affects vascular contractile response and glucocorticoid metabolism

Graham W. Souness[a,c], Andrew S. Brem[b,c], David J. Morris[a,c,*]

[a]*The Miriam Hospital (GWS and DJM), Providence, RI, USA*
[b]*Rhode Island Hospital (ASB), Providence, RI, USA*
[c]*Brown University School of Medicine, Providence, RI, USA*

Received 2 May 2001; received in revised form 26 June 2001; accepted 28 June 2001

Abstract

Glucocorticoids (GC's) are metabolized in vascular tissue by two isoforms of 11β-hydroxysteroid dehydrogenase (11β-HSD). 11β-HSD2 is unidirectional and metabolizes GC's to their respective inactive 11-dehydro derivatives. 11β-HSD1 is bi-directional, also possessing reductase activity and thus the ability to regenerate active GC from the 11-dehydro derivatives. In vascular tissue, GC's amplify the pressor responses to catecholamines and angiotensin II and may down-regulate certain depressor systems such as nitric oxide and prostaglandins. We hypothesize that both 11β-HSD2 and 11β-HSD1 regulate GC levels in vascular tissue and are part of additional mechanisms that control vascular tone. We examined the effects of specific antisense oligomers to 11β-HSD2 and 11β-HSD1 on GC metabolism and contractile response to phenylephrine (PE) in rat aortic rings. In aortic rings incubated (24 h) with corticosterone (B) (10 nmol/l) and 11β-HSD2 antisense (3 μmol/l), the contractile response to graded concentrations of PE (PE: 10 nmol/l − 1 μmol/l) were significantly ($P < 0.05$) increased compared to rings incubated with B and 11β-HSD2 nonsense. 11β-HSD1 antisense oligomers also enhanced the ability of B to amplify the contractile response to PE. In addition, 11β-HSD2 and 11β-HSD1 antisense also decreased the metabolism of B to 11-dehydro-B. 11-Dehydro-B (100 nmol/l) also amplified the contractile response to PE in aortic rings ($P < 0.01$), most likely due to the generation of active corticosterone by 11β-HSD1-reductase; this effect was significantly attenuated by 11β-HSD1 antisense. 11β-HSD1 antisense also caused a marked decrease in the metabolism of 11-dehydro-B back to B by 11β-HSD1-reductase. These findings underscore the importance of 11β-HSD2 and 11β-HSD1 in regulating local concentrations of GC's in vascular tissue. They also indicate that decreased 11β-HSD2 activity may be a possible mechanism in hypertension and that 11β-HSD1-reductase may be a possible target for anti-hypertensive therapy.

Keywords: Glucocorticoids; 11β-Hydroxysteroid dehydrogenase; Antisense; Vascular tissue

1. Introduction

Glucocorticoids (GC's) are known to play an important role in the regulation of vascular tone and blood pressure, but the biochemical mechanisms involved remain unclear. Glucocorticoid (GR) and mineralocorticoid receptors (MR) are present in aorta, mesenteric arteries and VSM cells in culture [1,2]. GC's can bind to and activate GR (and possibly MR) to potentiate the vasoconstrictive effects of both catecholamines and Ang II [3,4]. Tissue GC levels are regulated by two isoforms of the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) [5–7]. Human and rat vascular endothelial cells (EC) contain both 11β-HSD2 and 11β-HSD1 [8,9]. 11β-HSD2 uses NAD^+ as a co-factor and acts only as a dehydrogenase converting GC's to their inactive 11-dehydro metabolites [10]. It is generally understood that 11β-HSD2 operates to protect both MR and GR from excessive stimulation by GC's [11,12] and we and others have shown that GC's further amplify the contractile effects of phenylephrine (PE) and Ang II when 11β-HSD enzyme activity is inhibited [13–15].

11β-HSD1 uses $NADP^+$ as a co-factor and is bi-directional functioning as both a reductase and dehydrogenase [7]. Using RT-PCR, we have shown that rat vascular smooth muscle (VSM) cells only contain 11β-HSD1, which under 'physiologic conditions' acts largely as a reductase (3 reductase to 1 dehydrogenase) generating active corticosterone from inactive 11-dehydro-corticosterone [8,16]. We,

* Corresponding author. Tel.: +1-401-793-4231; fax: +1-401-274-5154.
E-mail address: dmorris@lifespan.org (D.J. Morris).

0039-128X/02/$ – see front matter
PII: S0039-128X(01)00148-9